FPN #781P

Chemotherapy sensitivity score based on ex vivo 3D tumor testing to predict clinical response for ovarian cancer patients

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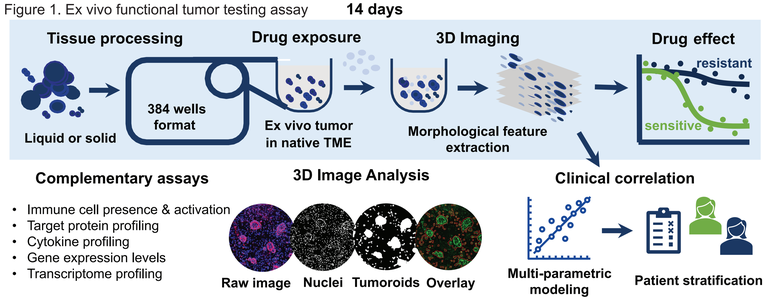
BACKGROUND

Precision medicine has brought effective novel therapy options over the past decades for cancer patients. However, treatment for high-grade serous ovarian cancer (HGSOC) is still based on platinum-containing chemotherapy. Approximately 30% of the patients with primary disease do not respond to this treatment, and the efficacy of systemic treatment drops steeply for patients with recurrent disease. Reliable tools to identify patients that will respond to therapy would contribute to better informed treatment decisions. We present a novel chemotherapy sensitivity score, based on ex vivo functional tumor testing, that classifies the predicted patients' response to chemotherapy prior to the start of treatment.

Figure 1. Ex vivo functional tumor testing assay



METHODS

- **TUMOVCA trial:** HGSOC patients, eligible for platinum-based neoadjuvant chemotherapy (NACT), were included in the trial between 2019 and 2022 in the Netherlands (IRB P18.032). Clinical data was collected including CA125 levels at baseline and after 2-4 courses of NACT.
- **Ex vivo functional tumor testing:** Tumor clusters enriched from fresh ascites were embedded in hydrogel and exposed to carboplatin, paclitaxel, three second-line therapies, PARPi, six immunotherapies and SEA as positve control for immunotherapy sensitivity. Assay plates were imaged in a high content screening platform, figure 1. Morphological features were extracted after image analysis and fitted as dose-response (Hill) curves.
- **Predictive model:** A Bayesian linear regression model was trained on the area under the curve (AUC) of carboplatin and paclitaxel sensitivity in the assay to predict the clinical CA125 half-life for 30 patients. The result was classified according to clinical standards: strong response (CA125 normalization to 35U/ml), moderate response (at least 50% reduction of CA125) or insensitive (less than 50% reduction or increase). For each second-line treatment the top 25% strongest responding samples were classified as sensitive while the bottom 25% were classified as resistant samples. Immune sensitivity was classified as no response (<10%), weak (10-20%), strong (20-50%) and very strong (>50%), based on percentage tumor killing.

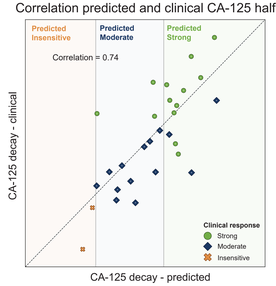
Table 1. Patient characteristics

Baseline characteristics (N=30)	
Age (mean, range)	67.5 (41-80)
Current diagnosis (%)	
HGSOC	27 (90)
Adenocarcinoma	3 (10)
Treatment (%)	
Carboplatin/Paclitaxel	30 (100)
Sample origin (%)	
Ascites	30 (100)
FIGO stage (%)	
IIIA	1 (3)
IIIC	21 (70)
IV	8 (27)
Surgery (%)	
No surgery	10 (33)
Interval debulking	19 (63)
Unknown	1 (3)
BRCA status (n, %)	
BRCA1 mutant	2 (7%)
BRCA2 mutant	1 (3%)
Wild-type	19 (63%)
Not tested	8 (27%)
CA125 (mean, range)	
Baseline	2774 (140-25000)
Interval	505 (12-3469)
Interval CA125 meas. (%)	
After 1 cycle	1 (3)
After 2 cycles	11 (37)
After 3 cycles	18 (60)
Interval in days (mean, range)	56 (19-170)

RESULTS

- **Assay performance:** The technical success rate for ascites samples with sufficient tumor content is 89%. The assay duration is 2 weeks from receipt of the fresh tissue sample.
- **Predictive performance:** The correlation coefficient between the predicted and actual CA125 half-life is 0.739 (R2 = 0.55) (Figure 2). This results in a classification accuracy of 80% (insensitive: 100% (n=2), moderate response: 80% (n=14), strong response: 80% (n=14)).
- **Benchmarking other treatments to standard of care:** 58% (8/14) of the samples that showed a strong response to standard-of-care, respond to at least one second-line therapy. For the moderate responders and insensitive patients, these percentages are 29% (4/14) and 50% (1/2), respectively. In addition, highly significant immune responses were observed in 35% of the samples.

Figure 2.
Correlation predicted and clinical CA-125 half life



CONCLUSIONS

- The presented chemotherapy sensitivity score based on ex vivo 3D tumor testing predicts clinical response to NACT with carboplatin and paclitaxel for HGSOC patients. In addition, relative sensitivity to other systemic therapy options were classified and benchmarked against the standard of care carboplatin - paclitaxel response.
- Ex vivo functional tumor testing enables better stratification of ovarian cancer patients for effective therapy options including chemo-, targeted-, and immunotherapies. In a planned prospective trial will establish the value of implementation of ex vivo functional testing in the clinical routine for ovarian cancer patients with incomplete platinum sensitivity or platinum refractory disease.

ONLINE POSTER

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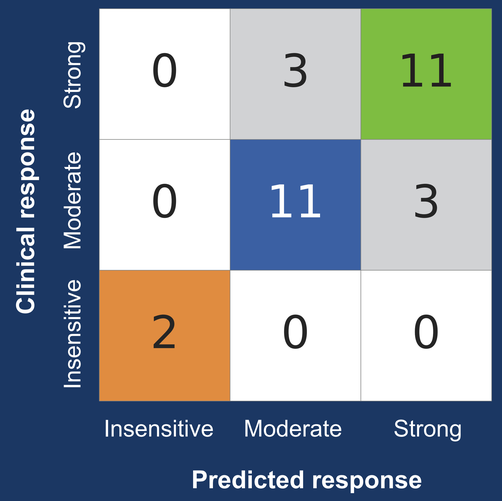
Ex vivo functional assay **predicts clinical response** to carboplatin-paclitaxel for **ovarian cancer** patients



Accuracy 80%
Negative prediction value 81-100%

Clinical response
- Strong
- Moderate
- Insensitive

Chemotherapy response
- Strong (top 25%)
- Moderate (median 50%)
- Insensitive (bottom 25%)
- Not tested

Numbers indicate AUC

Immune therapy response
- No → Strong
- Not tested
- * Highly significant

50% of the patients were classified as **strong responders** to second line and/or immunotherapies